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June 20, 2002

Assistant Commissioner for Patents
U.S. Dept. of Commerce / Patent & Trademark Office
Attn: Examiner Dwayne C. Jones, AU 1614
Washington, D.C. 20231

RE: Pat. Application #09/781,491
Clouatre, et al., Methods And Pharmaceutical Preparations For Normalizing Blood Pressure With (–)-Hydroxycitric Acid
Office Action Mailed 06/05/02

Dear Examiner Jones:

To avoid confusion, responses to the Office Action of 06/05/02 are provided under headings matching the numbering found in that action.

Office Action Response Item 4
In Applicants' arguments filed 5 March 2002 (Certified mailing by Applicants on 21 February 2002), it was noted that Shrivastava, et al. in US Patent #6,221,901 have defined their invention entirely in terms of magnesium (–)-hydroxycitrate and that in this context the (–)-hydroxycitrate is actually merely a ligand. The present Office Action claims that this is not the case and cites column 2, lines 9-11 in response, stressing that Shrivastava, et al. are directed to, "(–)-hydroxycitrate, namely magnesium (–)-hydroxycitrate." However, the Office Action left out the quite important distinction in that line, to wit, the claim by Shrivastava, et al. that " a subject of the present invention is a new compound [emphasis added] of (–)hydroxycitrate," which is then given as magnesium (–)-hydroxycitrate.

Indeed, Shrivastava, et al. had no choice but to claim that this is a new compound and not (–)-hydroxycitrate nor a property of (–)-hydroxycitrate because their claims regarding hypolipemia and the reduction in the synthesis of cholesterol (e.g., Claim 20) were already to be found abundantly in the literature with regard to (–)-hydroxycitrate. To put this differently, if Shrivastava, et al. do not in fact present (–)-hydroxycitrate as only a ligand for magnesium, then then various claims in the issued patent fail instantly in the face of prior art stretching back almost thirty years. One set of authors — and I stress this is only one of many sources — published the following in 1972:

> Fatty acid and cholesterol synthesis were inhibited in a similar manner by different (–)-hydroxycitrate concentrations. As *in vivo*, this compound appears to only partially inhibit fatty acid synthesis in the perfused organ.
>
> The similarity of the (–)-hydroxycitrate effect on cholesterol and fatty acid synthesis is suggestive of a common mechanism of inhibition, e.g. lowering of the cytoplasmic acetyl-CoA level. This assumption requires that both effects be abolished by replenishment of the acetyl-CoA pool by exogenous acetate. While

this was verified for fatty acid synthesis, ^{3}H-incorporation into cholesterol was not normalized by acetate addition."

Barth, C., J. Hackenschmidt, H. Ullmann, and K. Decker (1972). Inhibition of cholesterol synthesis by (–)-hydroxycitrate in perfused rat liver. Evidence for an extramitochondrial mevalonate synthesis from acetyl coenzyme A. **FEBS Letters** 22, 3 (May 1972) 343-346.

Similarly, Claim 19 regarding a reduction in the accumulation of lipids in vascular smooth muscles would appear to be a direct extension of work previously performed which showed that (–)-hydroxycitrate increases the catabolism of LDL cholesterol. The clear implication of this action under consensus medical thinking at the time of the filing of Shrivastava, et al. is that the collection of lipids in the artery wall would be reduced. Very curiously, no prior art of this nature is disclosed by Shrivastava, et al. and there is no discussion of these properties of (–)-hydroxycitrate in Shrivastava, et al.

The most significant finding in the present work is that overnight exposure of Hep G2 cells to the ATP citrate-lyase inhibitor (–)-hydroxicitrate results in an up-regulation of LDL receptor activity and LDL-receptor-dependent LDL catabolism.

Berkhout, Theo A., Louis M. Havekes, Nigel J. Pearce and Pieter H. E. Groot (1990). The effect of (–)-hydroxycitrate on the activity of the low-density-lipoprotein receptor and 3-hydroxy-3-methylglutaryl-CoA reductase levels in the human hepatoma cell line Hep G2. **Biochemistry Journal** 272, 1 (1990) 181-186.

It is noteworthy that in the BACKGROUND OF THE INVENTION, Shrivastava, et al. go to some lengths to indicate that (–)-hydroxycitrate itself does not have the properties of magnesium (–)-hydroxycitrate. The Office Actions claims that this is a recitation of the properties of (–)-hydroxycitrate, but instead this is exactly the opposite. Indeed, it is a recitation of properties which Shrivastava, et al. present as being desirable, although not found in present (–)-hydroxycitrate products. As the authors of that patent put it: "It would therefore be desirable to find a product endowed with the following properties...." Of course, Shrivastava, et al. claim that they fulfill this need with magnesium (–)-hydroxycitrate.

Shrivastava, et al. expressly deny what the Office Action says that they claim. The Office Action has essentially turned this contrast on its head and presented as accepted properties what Shrivastava, et al. actually indicate are not found in (–)-hydroxycitrate and therefore require their "new compound," namely magnesium (–)-hydroxycitrate. All the other citations to Shrivastava, et al. found in the Office Action, when examined, lead directly and inescapably to the same conclusion.

Moreover, the use of pharmacological studies by Shrivastava, et al. proves that they are not writing of the properties of (–)-hydroxycitrate, but rather of their so-called "new compound," magnesium (–)-hydroxycitrate. (I leave aside here the fact that the compound was not new, but rather was mentioned by Lowenstein in 1973 in US Patent #3,764,692.) As indicated in column 7, lines 14-23, Shrivastava, et al. expressly contrast (–)-hydroxycitrate as being totally ineffective, magnesium alone as being only partially effective, and magnesium (–)-hydroxycitrate as being very effective in protecting cell mortality. The fact that the authors are contrasting their magnesium with (–)-hydroxycitric acid ligand against either ligand or mineral alone is explicit:

> It can be observed firstly that the (–)hydroxycitrate alone has no protective effect on cell mortality. Magnesium alone reduces this mortality very slightly, whereas magnesium (–)hydroxycitrate has a more protective effect.
>
> The magnesium (–)hydroxycitrate greatly reduces cell mortality (70.+-.8%), proving the protective effect of this product against oxidation damage.
>
> As regards the accumulation of lipids and cell proliferation, a very significant increase in the effects of magnesium (–)hydroxycitrate is observed with respect to (–)hydroxycitrate or magnesium.

In passing, I note two of the many oddities of this trial. First, the ligand of the magnesium tested by itself is not given, yet without a ligand magnesium is virtually insoluble in these culture mediums and, likewise, magneiusm had to be added with a ligand attached. Second, if (–)-hydroxycitrate has no antioxidant properties, as claimed by Shrivastava, et al., how is it that there is a Japanese patent with the title, "Use of hydroxycitric acid as an antioxidant?" (INVENTOR(S)- Abu, Takahiko; Komai, Shoichi)

At no point do Shrivastava, et al. indicate that magnesium (–)-hydroxycitrate is a preferred embodiment amongst other possible embodiments, although if the interpretation given in the Office Action were correct, this would be expected. At every juncture, Shrivastava, et al. contrast magnesium (–)-hydroxycitrate with both (–)-hydroxycitrate and magnesium. The reason that they do not list magnesium (–)-hydroxycitrate as a preferred embodiment amongst other possible embodiments is that it is the only form of (–)-hydroxycitrate for which they are making any claim, hence it is their only embodiment of the compound. Yet in this use, (–)-hydroxycitric acid cannot be but a ligand for magnesium.

Actually, there is one glaring exception to the foregoing. Shrivastava, et al. (column 8, lines 30-37) fail to test either magnesium or (–)-hydroxycitrate as anti-hypertensive agents, as would have been expected — no, required — to support their patent claims. They did not test the former because magnesium had long been known as a hypotensive agent and this would have spoiled their results. They did not test the latter because they had no idea — and no expectation — that (–)-hydroxycitrate has hypotensive effects. Therefore, the claim of Shrivastava, et al. must be for magnesium (–)-hydroxycitrate sole, that is, for magnesium with hydroxycitric acid as a ligand.

Moreover, the results of Shrivastava, et al were derived by giving the test animals such

massive amounts of the compound that these animals almost immediately became hypotensive due to osmotic diarrhea. As Harry G. Preuss, MD, Professor of Medicine at Georgetown University, said to me with regard to the trial by Shrivastava, et al., "Why did they not just give the animals milk of magnesia? The result would have been the same." As a matter of simple logic, if it is the case that using magnesium in the amounts cited in the Shrivastava, et al. patent can account for the observed effect, then there can be no logical claim that the patent covers magnesium (–)-hydroxycitrate as a blood pressure-lowering agent. Quite simply, the ant-hypertensive claim being put forth is not supported by the evidence found in the patent itself.

According to *In re May*, 574 F.2d 1082, 1090, 197 USPQ 601, 607 (CCPA 1978), it is not allowable under the doctrine of inherency to patent a new use which relies upon a known property of a compound (let alone, of course, patent a known use of a known property). Magnesium is a known anti-hypertensive agent with various proposed mechanisms, and this was true long before Shrivastava, et al.. Anyone skilled in the art would expect acceptable pharmaceutical salts of magnesium to have the same action to a greater or lesser degree. Yet Shrivastava, et al. with regard to their anti-hypertensive claim do not so much as even attempt to demonstrate that it is not anticipated by the prior art readily available on magnesium. Similarly, Shrivastava, et al. do not make a claim regarding (–)-hydroxycitric acid and its derivatives *per se*, which would be new, inasmuch as Shrivastava, et al. would have it that magnesium (–)-hydroxycitrate is itself a new compound, a claim contradicted by Lowenstein, cited above. Finally, Shrivastava, et al., nevertheless, must and do insist that magnesium (–)-hydroxycitrate is a new compound and not merely a salt of (–)-hydroxycitrate because otherwise they would be roundly anticipated in their claims, specifically Claims 19 and 20.

In contrast, Applicants claim that hypotensive properties are to be found directly in (–)-hydroxycitric acid and its pharmaceutically acceptable salts and do not depend upon the metal being attached to the ligand. Likewise, as required in *In re May*, 574 F.2d 1082, 1090, 197 USPQ 601, 607 (CCPA 1978), Applicants provide novel mechanisms in evidence of this claim. Our claim has now been supported independently by the work of others. Dr. Preuss, mentioned already, recently showed that using a mostly calcium salt of (–)-hydroxycitrate (SC) at approximately one half the dosage employed by Shrivastava, et al. lowers blood pressure in hypertensive rats starting the first week. [Dose was 200-400 mg/day given to 700-1,100 gram very old Zucker obese rats. Other active arms included chromium (NBC) and an immune stimulant (SX).] Calcium, as opposed to magnesium, does not cause diarrhea and is not known as having any appreciable effect upon blood pressure. I include a graph of Dr. Preuss' results which he faxed to me. It will be seen that blood pressure dropped with all compounds beginning the first week; at the end of six weeks the results of all compounds were similar.

In light of the above evidence and argument, it is indisputable that

a) Shrivastava, et al. make no claims for any form of hydroxycitrate or hydroxycitric acid other than magnesium (–)-hydroxycitrate inasmuch as Shrivastava, et al. themselves explicitly insist upon this distinction
b) Shrivastava, et al. expressly contrast magnesium (–)-hydroxycitrate with both magnesium and hydroxycitric acid throughout most of their patent

c) Shrivastava, et al. provide neither evidence nor argument that magnesium (–)-hydroxycitrate is superior in any way to either magnesium or hydroxycitric acid as a hypotensive agent
d) The literature is filled with prior art suggesting the hypotensive actions of magnesium
e) Prior to Clouatre and Dunn, there is no evidence from any source that (–)-hydroxycitric acid itself has hypotensive actions nor are mechanisms proposed to account for this effect
f) The obvious conclusion is that Shrivastava, et al. are making claims for magnesium as having special properties when (–)-hydroxycitric acid is its ligand, with the implication that (–)-hydroxycitric acid magnifies the properties already known for magnesium due merely to its carrier properties as a ligand, yet even in this regard those inventors have failed to offer the evidence and argument necessary for any claim to anti-hypertensive properties
g) Hence, Shrivastava, et al. actually do not have a right to any claim regarding anti-hypertensive actions, let alone a claim upon any form of (–)-hydroxycitric acid, its salts or its derivatives in this regard

Office Action Response Item 5

The Office Action's response to Applicants' arguments regarding European Patent Application 803,202 A2 by Littera, et al. is not logically satisfying. In fact, there is no obvious reason that the Office Action even cites Littera, et al. The current Office Action refers back to the earlier Office Action mailed 01/31/02. In that Action it is indicated that Littera, et al. (p. 2, lines 7-12 and 50-52) propose treating various disorders, including hypertension. But this not the case. First, lines 1- 10 lay out the invention as being one directed toward remedying hypercholesteremia and obesity. Lines 11-12 are very poorly worded and actually say that the invention is efficacious in weight reducing programs aimed at calorie restriction in obese subjects and in the treatment of hypertension. These lines do not directly claim anti-hypertensive effects with regard to the indicated composition. Furthermore, despite the remarks in the earlier Office Action, there is no reference to hypertension or its treatment in lines 50-52 of Littera, et al.

Present Applicants' position that Littera, et al. has no bearing is proven by the fact that Littera, et al. nowhere else in the entire document other than in line 12 mention hypertension or its treatment. There are no data, no discussion and, most assuredly, no claims. Everywhere, the remarks, as on page 3 in line 44, are about "hypocholesteremic and sugar absorption reducing activity." As indicated above, the hypocholesteremic actions of (–)-hydroxycitrate were published at least as early as 1972. Those of chromium, similarly, had long been established by the time of the filing of the Littera, et al. application. Regarding "sugar absorption reducing activity," there is no evidence anywhere — most certainly not in this European application — that any of these compounds perform this action.

In light of the preceding remarks, there is absolutely no reason to consider Littera, et al. in the context of the Application by Clouatre and Dunn. Again, in Literra, et al. document there are no data, no discussion and no claims regarding hypertension or its treatment.

Even were there remarks in Littera, et al. as represented in the Office Actions, these would not support the end to which the Office Action would direct them. Present Applicants' claim is that (–)-hydroxycitrate has hypotensive actions by itself. Littera, et al. have cobbled together items (chromium and chitosan) which are a) already known to lower blood pressure, b) known to so reduce the uptake of hydroxycitric acid that no conclusion could possibly be drawn as to any benefit from the hydroxycitric acid component. As above, as a matter of simple logic, if it is the case that using chromium in the amounts cited in Littera, et al. can account for the observed effect, then there can be no logical claim that the patent covers (–)hydroxycitrate as a blood pressure-lowering agent. The claim being put forth is not supported by the evidence found in the patent itself and there is neither a specific claim nor evidence regarding the actions of (–)hydroxycitrate. In support of the point being made, the animal data supplied by Dr. Preuss has an arm in which chromium is the active ingredient. It will be noted that the chromium has a very strong early effect, although the effect of the calcium (–)-hydroxycitrate is equal to that of the chromium in this model at six weeks.

As for the comment in the Office Action regarding "comprising" as "open-claim language," this turns the logic covering such language on its head. To list all agents together, as in Littera, et al., means that all the agents must be used together to have the indicated effect. By way of contrast, Applicants, first of all, have shown directly that only a form of (–)-hydroxycitrate is required, for which see our examples. This has now been confirmed independently by Dr. Preuss, as mentioned above. Our presentation in the Application is of a composition in which the sole active ingredient is a form of (–)-hydroxycitric acid. Second, regarding the word "comprising" in our claims, at most all that might be said is that we have not excluded that other items might be added, not that we require the actions of other items.

Hence, there is a direct and stark contrast between the claims of the Applicants and those of Littera, et al. [("Comprising' is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim."); Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948) ("comprising" leaves the "claim open for the inclusion of unspecified ingredients even in major amounts").] Applicants claim that only a form of (–)-hydroxycitrate is required. However, Littera et al. require, as well, both chromium and chitosan, yet have not distinguished what is additive and are unaware of the fact that the chitosan will bind up and make pharmacologically unavailable any form of (–)-hydroxycitric acid, whether free form or salt. In other words, there is no support in Littera, et al. for the claims being made inasmuch as, from a pharmaceutical perspective, only the chromium and the chitosan can possibly be active in the invention proposed by Littera, et al. Clear evidence of the lack of bioavailability of a chitosan/hydroxycitrate mixture was provided in our response filed 5 March 2002 based upon independent and published research appearing in a peer reviewed journal.

Finally, one should be aware of the absurdity of the dosage of (–)-hydroxycitrate being recommended in Littera, et al. Chromium compounds act upon insulin receptors, and therefore quite tiny amounts may have some benefit. Such is not true of (–)-hydroxycitrate (or, for that

matter, chitosan). (–)-Hydroxycitrate competitively inhibits an enzyme in the cytoplasm of the cell. Its activity requires gram amounts, not milligrams. Trials by reputable independent researchers and published in peer reviewed journals have shown conclusively that under clinical conditions similar to those claimed by Littera, et al., 1.5 grams of the compound per day does not lead to weight loss. (Heymsfield SB, et al. Garcinia cambogia (hydroxycitric acid) as a potential antiobesity agent: a randomized controlled trial. JAMA 1998 Nov 11;280(18):1596-600) Littera, et al. are claiming an effect with 55 mg per day when thirty times that amount, in reality, is not efficacious. This, moreover, is without giving the (–)-hydroxycitrate together with a compound (chitosan) which will simply bind it and lead to its excretion unabsorbed. In contrast, weight loss similar to that indicated by Littera, et al. was reported as far back as 1973 for the simple combination of (–)-hydroxycitrate (750 mg/day) and chromium (200 mcg/day). (Conte, Anthony A. A non-prescription alternative in weight reduction therapy. The Bariatrician 1993 Summer:17-19.) Both weight loss and broad blood lipids lowering results for a mixture of chromium and (–)-hydroxycitrate were presented and widely distributed in July 1995 at the annual convention of the Nutritional and Natural Foods Association in Las Vegas, Nevada, albeit these results by Badmaev V, Majeed M and Conte AA were only published this year in the journal Nutraceutials Jan/Feb 2002:10-14.

In sum, Littera, et al. has no relevance to the Application of Clouatre and Dunn because Littera, et al., teaches nothing regarding the hypotensive actions of (–)-hydroxycitrate. Indeed, a close reading shows that Littera, et al. do not even teach such regarding their overall composition. In that document there are no data, no discussion and no claims regarding hypertension or its treatment. Neither can the other arguments put forth in the Office Action based upon Littera, et al. withstand scrutiny.

Claim Rejections - 35 USC § 102 and 103

Inasmuch as these rejections are based upon Responses 4 and 5 above, they now must be reconsidered and removed.

The present Inventors (Clouatre and Dunn) find it necessary to observe the following: With regard to anti-hypertensive actions, neither Shrivastava, et al. nor Littera, et al. make any claims which were not known long in advance of their filings. Magnesium's role in blood pressure regulation is classic and chromium, likewise, had been examined on this topic long before either Shrivastava, et al. or Littera, et al.

One possessed of even moderate knowledge of nutrition at the time of the filing of Shrivastava, et al. could have observed that any tolerable salt of magnesium likely would lower elevated blood pressure in various animal models. Shrivastava, et al., of course, would not have been able to patent magnesium *per se* for blood pressure regulation. The oddity is that they were allowed claims regarding a magnesium salt for this purpose. They did not show that this salt works better than any of the many other salts of magnesium which are available. Nor did they suggest a novel and unexpected mechanism. In fact, there is neither discussion nor evidence at all to be found in Shrivastava, et al. on the novelty of the salt or the novelty of a mechanism of action with regard to lowering blood pressure. Surely at least one of these is required for a patent? Applicants stand by our observation made above that Shrivastava, et al. actually do not

have a right to any claim regarding anti-hypertensive actions, let alone a claim upon any form of (–)-hydroxycitric acid, its salts or its derivatives in this regard.

Similarly, Littera, et al. do not the demonstrate superiority of the proposed mixture of chitosan, hydroxycitrate and organic chromium to a simpler mixture of the chitosan plus the chromium nor, with regard to blood pressure, versus chromium alone. Again, where is the novelty of the mixture versus just one of its listed ingredients, i.e., chromium? Where is the new mechanism of action? Where is there anything which should be patentable? For that matter, where is there any evidence or discussion at all regarding hypertension? In fact, Littera, et al. has no bearing whatsoever upon the present Application.

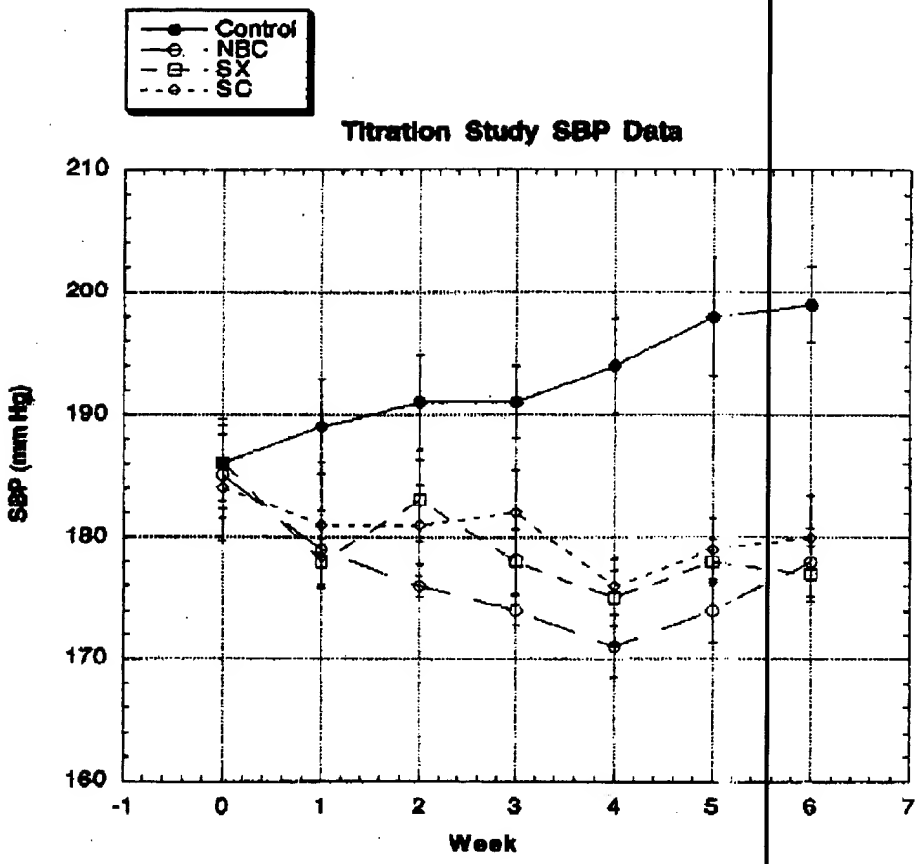
In distinction to both Shrivastava, et al. and Littera, et al., the current Applicants have supplied both novel and unexpected mechanisms of action (influence on insulin and glucocorticoids) and a novel employment of the compound (–)-hydroxycitrate.

Sincerely,

Dallas L. Clouatre

Dallas L. Clouatre, Ph.D.

Enclosures



Press data